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Conference Report

Opportunities and challenges in ovarian cancer research, a perspective from the 11th Ovarian cancer action/HHMT Forum, Lake Como, March 2007

Abstract

Advances in surgery and chemotherapy have improved the 5-year survival for patients with epithelial ovarian cancer, but have not impacted on the ultimate rate of cure in a disease that is diagnosed in late stage and that recurs in the majority of patients. "Omic" technologies promise to define genetically driven aberrant signaling pathways in malignant cells, provided that bioinformatic expertise can be focused on a cancer that is neither common nor rare. Molecular therapeutics must be linked to molecular diagnostics to permit individualized therapy. Not only epithelial cancer cells but also stroma, vasculature and the immune response must be targeted. Closer collaboration between academic institutions, biotech and pharma will be required to facilitate this process and to interest the private sector in an orphan disease. New preclinical models may permit more efficient development of drugs and siRNA that can target dormant drug resistant stem cells. Strategies must be developed to deal with the heterogeneity of different grades and histotypes. Identification of women at increased risk will facilitate prevention and early detection in subsets of patients. BRCA1/2 might be sequenced in all ovarian cancer patients to identify new kindreds. Epidemiologic algorithms are being developed and validated. Awareness must be raised that oral contraceptives can reduce risk of developing ovarian cancer by 50%. Early detection is likely to require panels of complementary biomarkers, analyzed by sophisticated statistical techniques, to improve sensitivity while maintaining extremely high specificity. As ovarian cancer becomes a chronic disease, greater emphasis will be placed on the challenges facing survivors.

Keywords: Ovarian cancer; Genomics; Drug development; Early detection; Risk

Despite advances over the last three decades in cytoreductive surgery and combination chemotherapy, ovarian cancer remains a significant threat to women internationally. Ovarian cancer is the fourth most common cancer in women and accounts for 204,000 new cancer cases and 125,000 deaths each year worldwide [1]. Ovarian cancer has the highest mortality of all cancers of the female reproductive system, which reflects, in part, late diagnosis and a lack of proven ovarian cancer screening tests, as well as the development of drug-resistant cancer cells.

Overall, 5-year survival for all stages has increased in the United States from 37% in the 1970s to 45% in the 1990s [2]. Treatment in dedicated centers with specialized surgeons offers a benefit in survival for women with ovarian cancer, and advances in chemotherapy permit women to live for 5 and sometimes even 10 years. Despite this progress, recent empirical trials comparing doublets and triplets of active drugs in every possible combination may prove to be essentially negative, suggesting we need novel compounds and strategies to make a difference to the lives of women with ovarian cancer. It is therefore important to take stock of the current research programs and question what are the major challenges and opportunities in ovarian cancer, in particular in the next 5 years.

Identify women at risk

If prevention strategies are to be developed, more sophisticated markers for risk are needed to permit efficient trials of chemoprevention or prophylactic oophorectomy in subsets of women. These markers will come from studies of mutant genes, SNPs, epidemiology and lifestyle. Aside from genetic profiling, there may be reproductive or environmental risk factors which could be combined to identify women at increased risk for the disease. Such women might be candidates for more intensive screening or chemo- or immunoprevention.

A combination of demographic, reproductive and environmental risk factors might be used to develop a model that would more accurately predict risk. One preliminary algorithm using seven risk factors (age over 45; long-term genital talc use; family history of ovarian cancer or early onset breast cancer; Jewish ethnicity; no oral contraceptive (OC) use; no livebirths; no breastfeeding; no tubal ligation) showed that women with six to seven of these events have an OR of 7.59 [3]. Combining these data with other epidemiological data, such as height, premenopausal obesity, and emerging data from dietary studies, could produce a useful predictive algorithm within the next year. Future epidemiological

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research must take into account each histologic type. Retrospective methods for testing any new algorithm must be developed, as it is unlikely that a prospective trial would be economically viable.

Up to 15% of ovarian cancers are familial and, in some populations (e.g. Ashkenazi Jews), this figure may be even higher, and most of these are related to BRCA1 or BRCA2 mutations. Several delegates felt that convincing data now support screening all women with ovarian cancer for mutations of these genes, if the barrier of cost could be overcome. Identifying BRCA carriers not only allows the possibility of prevention within a high-risk subgroup, but may also permit choice of more effective chemotherapy (e.g., the use of PARP inhibitors).

Oral contraceptives (OCs) are powerful chemopreventative agents against ovarian cancer. The use of OCs for 10 years can lead to a 50% risk reduction for ovarian cancer [4]. Among high-risk women, this would appear to be a highly attractive option. The protective effect of OC on ovarian cancer risk corresponds to the avoidance of 3000–5000 ovarian cancers (and 2000–3000 deaths) per year in Europe. However, the use of OCs as a chemopreventative appears to be rarely mentioned when women are making contraceptive decisions and perhaps awareness of their use as a chemopreventative should be raised among general practitioners.

Contrary to current understanding, at least in young women (30–35 years of age) with BRCA1 mutations, OC use may actually decrease the risk of breast cancer [5], although use at a later age may increase the risk of breast cancer [6]. If all BRCA carriers took preventative measures (oophorectomy, use of OC, breastfeeding, having children), the overall ovarian cancer mortality could be reduced up to 12% [7]. It should be noted that there remains a small risk of developing ovarian cancer (0.2% a year) even after oophorectomy [8].

Early detection

There is currently no established profile of biological markers, epidemiological markers, imaging techniques or their combination that has been shown to have both adequate specificity and sensitivity to screen the general population for early stage ovarian cancer. Rising CA125 and transvaginal ultrasound has the requisite specificity, but it remains to be seen whether there is sufficient sensitivity and lead-time. The UK Collaborative Trial of Ovarian Cancer Screening Study (UKCTOCS) has accrued more than 200,000 women and will conclude in 2011 [9]. Whether this study is positive or negative, multiple markers will be required to achieve optimal sensitivity, given the heterogeneity of ovarian cancer.

Progress has been made in identifying panels of biomarkers that detect a greater fraction of patients with stage I cancer than can be identified with CA125 alone. Promising candidates include HE4, mesothelin, the kallikreins and proteomic markers [10]. The Luminex multiplex technology permits the simultaneous assay of more than 50 analytes with very small amounts of serum that should facilitate identification and validation of optimal panels with the limited amounts of serum archived from screening studies such as the UKCTOCS in the United Kingdom and the PLCO trial in the United States [11]. The four Ovarian SPOREs in the United States have banded together to evaluate novel markers using the PLCO resource.

Identify the precursor lesion

Ovarian cancers can arise from multiple sites in addition to the ovarian surface. It has been suggested that many cancers arise from subserosal cysts. Endometriosis with atypia may be the precursor lesion for many endometrioid ovarian cancers [12]. Cancers with similar morphology and clinical behavior can arise from the fallopian tube and peritoneum [13]. Although there appear to be different sites, at least anatomically, it remains to be clarified whether these regions have the same stem cell/precursor or phenotype or genetic changes.

An important line of enquiry is the relationship between normal epithelial stem cells and cancer stem cells. Whether putative cancer stem cells represent the cell of origin or a re-populating cell, which itself may not be a derivative of the cell of origin, remains to be elucidated. Pre-malignant lesions have not yet been clearly demonstrated, but the identification of ovarian dysplasia/carcinoma in situ would have enormous implications for early detection.

Subtypes of ovarian cancer

More attention should be given to non-serous subtypes and low-grade cancers. In the current genomic era, clinicians and laboratory investigators should move away from conventional histological typing and toward gene expression and proteomic profiling. The recent decision to eliminate borderline (low malignant potential) tumors from ovarian cancer statistics has led to an arbitrary decrease in the prevalence of the disease and a worsening of mortality. Given the possible impact on research funding and the interest of pharmaceutical companies in developing useful drugs, this decision should be reconsidered.

Target the important mutations/develop new therapeutic agents and strategies

Novel targets have been identified in ovarian cancer. Mechanistic studies of human embryology have suggested Mullerian Inhibiting Substance as a target for therapy [14]. Liposomal delivery of siRNA appears most promising and may soon permit translation to the clinic allowing numerous targets to be attacked [15]. Whether or not new candidates will be revealed through Cancer Genome Project remains to be determined. Greater emphasis might be placed on defining aberrant pathways rather than focusing only on mutations in individual signaling molecules. Inhibitors are, for example, being sought for the JAK–Stat pathway that is activated in a majority of ovarian cancers [16]. The major challenge is to translate promising biological information to clinical trials.

Target the microenvironment

Traditional targets for anti-cancer therapy have been gain-of-function mutations or activated pathways within the tumor. However, it is likely that the tumor has some sort of rewiring mechanism enabling it to circumvent any blocked pathway by activating another mechanism, thus avoiding cell death and allowing continued tumor growth. One of the main problems with ovarian cancer is not the lack of initially effective treatment, as platinum compounds and taxanes produce regression in 70% of cases, but rather the subsequent development of drug resistance.

Considering the complexity of molecular alterations in the signaling networks of malignant cells, additional and complementary targets can be found in the tumor microenvironment. Half of the cells in ovarian tumor nodules are non-malignant stromal cells and the majority of these cells are thought to promote growth and spread of the epithelial ovarian cancer cells. Two targets of particular interest are cancer-related inflammation and the neovasculature of ovarian tumors. Effective anti-inflammatory cytokine drugs have already been developed and are widely used in humans for a range of severe chronic inflammatory diseases. Anti-inflammatory drugs and antibodies can now be tested in cancer. TNF á, IL-6 and their signaling pathways are particularly important potential targets in ovarian cancer [17,18]. Phase I/II clinical trials of antagonists of these inflammatory cytokines are underway and further studies combining these agents with conventional or novel targeted therapies will commence shortly [19]. The implication of IL-6 in resistance to conventional cytotoxic drugs provides a rationale for combining IL-6 antagonists and chemotherapy [20].

The anti-VEGF antibody bevacizumab (Avastin) has shown great promise in clinical trials to date as an antivascular and antitumor agent that can stabilize ovarian cancer growth for up to 5 months in half of patients [21]. Stabilizing disease using antibody maintenance therapy every 2–3 weeks is, however, costly. If less intensive schedules can be shown to be as effective, the costs involved may turn out to be not as prohibitive as first thought. Trials in the future are likely to target not only endothelial cells but also the pericytes that surround and support tumor vessels.

Immunotherapy

Because specific immunotherapy has not traditionally been of great interest to pharmaceutical companies, academe can play a unique role in this area, provided that funding can be found through government grants or philanthropy. Vaccines, cellular adoptive therapy and immunoregulation with antibodies are all approaches applicable to ovarian cancer [22].

Effective vaccines depend upon the identification and full characterization of the antigens associated with ovarian cancer. Utilization of dominant epitopes of ovarian tumor associated antigens and their presentation by appropriately stimulated dendritic cells [23] could achieve responses comparable to those now observed in patients with melanoma and leukemia following treatment with vaccines.

Cellular adoptive therapy can now be tested as sophisticated methods have been developed to expand antigen-specific T cells ex vivo and to promote their persistence in vivo following transfer. Given the logistical complexity and expense of this approach, substantial therapeutic benefit will be required to justify routine clinical use. Greater efficacy may be achieved through depletion of T regulatory cells or immunoregulation with anti-CTLA4 antibodies.

Immunotherapy is likely to be most effective in combination with agents that can reduce the burden of ovarian cancer cells. If vaccines are to be used, the tumor microenvironment must be modulated with other agents to avoid non-specific immunosuppression or the induction of specific tolerance. The off-target effects of molecular therapy must also be understood. The use of immunotherapy will require the consideration of the immunocompetence of patients with ovarian cancer after treatment with chemotherapy, particularly repeated cycles of carboplatin. Even when a vaccine containing an appropriate epitope engages appropriate antigen presenting cells, patients may not have an adequate T cell repertoire to mount an effective response. Some schedules of chemotherapy may not suppress and may even enhance the response to vaccines. Many targets for therapeutic vaccine development may eventually be used in a preventative strategy, where the immune response is largely intact and the burden of transformed and transforming cells is minimal.

New models

Developing more predictive preclinical models could improve the rate of success for drugs in the clinic. A drug that lacks activity in animal models is unlikely to succeed in clinical trials, but efficacy in our current preclinical models does not assure efficacy in humans. Human cancer xenografts are established from individual patients and multiple xenograft models may be required to take into account the heterogeneity from cancer to cancer at a molecular level. Given the large number of cell lines available, ovarian cancer xenografts might be matched more closely to the phenotype of cancers taken directly from patients. Orthotopic (intraperitoneal) models may be more predictive than subcutaneous xenografts [24]. Regression may be more predictive than stabilization of human ovarian cancer cell growth in culture or in xenografts.

In recent studies, an ovarian cancer xenograft model has been developed for tumor dormancy and autophagy [25]. Expression of the imprinted tumor suppressor gene ARHI (DIRAS3) from a tet-inducible promoter induces autophagy in cell culture and in xenografts. Autophagic cells die in cell culture, but survive as xenografts in immunocompromised mice and grow promptly when ARHI is down-regulated. The availability of this model should permit development of techniques to image autophagic cells and to target proteins required for survival of dormant cancer cells.

The immunocompetence of genetically manipulated mouse models permit exploration of the autochthonous immune response, but the cost and impact on intellectual property discourage their use in early-stage drug development. Transgenics may have their greatest value in defining the optimal use of more established agents. A more cost-effective option is to make transplantable cell lines from genetically modified mice. Despite the apparent advantages of mouse models, there are still no data to suggest they are any better than orthotopic xenograft models. Furthermore, the use of the mouse may have contributed to the current failure rate we see in getting drugs to successful trial.

At the end of the drug development pathway, molecular therapeutics and molecular diagnostics need to be linked in clinical trials. Biopsies for molecular pathology and images for molecular diagnostics will be needed before and during treatment. Clinical trials should occur at an earlier phase of drug development. If we are to evaluate the large number of new drugs and combinations, ovarian cancer patients must be encouraged to participate in clinical trials. Smarter trials with adaptive design may require fewer patients to achieve an endpoint. Since ovarian cancer is thought of as a rare cancer, funding for trials remains limited, but it is likely that the emergence of consortia of groups, such as the SPOREs and the Ovarian cancer action/HHMT collaborations in the UK, who are capable of sophisticated studies, will drive this forward.

Future experimental design must take into account the strengths and weaknesses of each model and the choice of model should reflect the hypothesis being tested. Ultimately, the only model that matters is the human patient.

Omics

Ovarian cancer is one of three tumor types chosen for genomic and epigenomic analysis in The Cancer Genome Atlas project (TCGA), a $100 million joint pilot project of the NCI and Human Genome Research Institute. Five hundred serous ovarian carcinomas will be studied, yielding a wealth of "omic" data potentially useful for risk assessment, early detection, and patient management. Complementing that effort are other projects that have already yielded useful omic information. In that regard, the most extensively profiled set of cells in existence is the panel of 60 diverse human cancer cell lines (the NCI-60) used by the US NCI to screen more than 100,000 chemical compounds plus natural products for anticancer activity. Those cells have been profiled at the DNA, RNA, protein, chromosomal, functional, and pharmacological levels. One outcome of that "integromic" [26] enterprise has been a rationale for treatment of a subset of ovarian cancers with the bacterial enzyme-drug L-asparaginase, which has been used since the early 1970s to treat acute lymphoblastic leukemia [27].

As we try to exploit the potential of high-throughput molecular profiling studies, for example, using microarrays to assess ovarian cancers, the role of biostatistics has become increasingly prominent. Given the complexities of the high-dimensional data produced [28], no software can substitute for professional statistical judgment—preferably exercised in close collaboration with the biologists on the project. It is important that statistical expertise be involved in the design, conduct, and analysis of such projects. The need for expertise in bioinformatics has also increased dramatically. Biological interpretation is the hardest part of any molecular profiling project, and the rapidly increasing information resources publicly available for the interpretive process represent a gold mine for those who know how to exploit them. The principal skill set required of a bioinformaticist is that of the biologist who has decided that he or she prefers the computer to the bench. It can be argued that there is little sense in spending large sums on high technology without funding the human resources required for statistical analysis and biological interpretation of the resulting data. Nonetheless, expertise in those disciplines remains in woefully short supply at most biomedical institutions.

Challenges of drug development

Targeted therapy has been validated in several different forms of cancer by the development of such drugs as Herceptin, Gleevec, Tarceva, and Avastin. The use of these drugs signals a move toward personalized molecular cancer medicine, but their impact on survival to date is often only modest. The use of biomarkers for patient selection, proof of concept and optimizing therapy has been central to the development of Herceptin and Gleevec, but only recently applied to other targeted therapies. There are more than 350 cancer genes and multiple molecular abnormalities present in many cancers. Many pathways are still undrugged and resistance to validated drugs remains a common problem.

Combinatorial approaches will be required and selecting the optimal combination of therapies is difficult, given the expense and duration of clinical trials and lack of reliable animal models. Computational and systems-based approaches will be required but are still embryonic. To tackle problems of efficacy, scientists need to select better targets, develop more predictive animal models and use predictive biomarkers to select patients. These are all areas already identified in ovarian cancer research as key areas to focus on. Many cancer drugs fail late in development and it is important to make tough early decisions and have a clear pharmacologic audit trail.

To accelerate the development of effective drugs against ovarian cancer, it is important to recognise why so many oncology drugs fail in clinical trials [29]. In 2000, only 5% of drugs tested showed any success in the clinic. The reasons for failure included inappropriate pharmacokinetics or bioavailability (~8% attrition), toxicity (~30%), lack of efficacy (~27%), and inadequate economic return (~27%). Increased awareness of the issues involved in pharmacokinetics has reduced the contribution to failure from around 40% in 1991 to less than 10% in 2000.

Although there is some capacity for independent drug development in academia based on fundamental research, more effective collaboration with biotech and pharma is needed to develop drugs that would treat ovarian cancer more effectively. Greater academic involvement will mitigate early risk and academia can play a role in early stage validation and drug discovery. There is the potential for academia to play more of a role, although this requires some investment in academia, as well as assistance in the GMP production of drugs and antibodies. It is possible for collaborations between academia and small biotechs to take molecules through to phase II trials and show activity, and this might encourage pharma to become interested in these targets.

Economically, large pharmaceuticals are currently less interested in moderately rare (niche) cancers such as ovarian cancer, and this may be preventing important clinically relevant molecules moving through to clinical trial. However, blockbuster business models may be unsustainable and alternative non-blockbuster business models need to be developed. Small biotechs and venture capitalists are looking for a niche, and better communication is required to convince the industry that the data regarding ovarian cancer is sufficient to warrant further investigation. Practical mechanisms, such as workshops that introduce industry to clinically relevant areas of academia, are already playing a role in increased communication.

Key recommendations

- Address the "omic" challenge (sponsor workshops, train more bioinformaticists)
- Develop ways to work with pharma and to interest companies in ovarian cancer as a target (sponsor workshops, invite them to future meetings)
- Develop and validate appropriate preclinical and clinical models to test hypothesis-driven drug development
- Screen women with ovarian cancer for BRCA1/2
- Raise awareness of oral contraceptive use in high-risk women/carriers of BRCA and in women at conventional risk
- Combine epidemiological data to get a decent algorithm for risk
- Invest in ovarian cancer stem cell research
- Restore tumors of low malignant potential to ovarian cancer statistics
- Explore distinctive strategies for prevention, detection and treatment for ovarian cancers of different grade and histotype
- Continue to target the ovarian cancer microenvironment
- Identify methods to support full time ovarian cancer research
- Encourage women to participate in clinical trials.

Abstracts of the papers presented at the Ovariancancer action/HHMT forum are available via the Ovarian cancer action Website: www.ovarian.org.uk.

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